

REMARKS

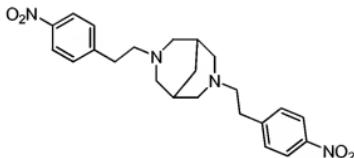
Claims 1 and 3-13 are pending in the application. A copy of the presently pending claims is provided on pages 2-5 for the convenience of the Office.

35 U.S.C. § 103(a)

Claims 1 and 3-13 are rejected for allegedly being unpatentable over Andersson et al., WO 02/04446 ("Andersson") in view of Rai et al., "Estimating Heterotrophic Production of Bacterioplankton by Measuring Tritiated Thymidine", *Pelagic Ecol. Methodol.* 18: 163-167 (2002) ("Rai").

[1] The Rejection

The Office relies upon the disclosure of the following compound in Andersson (Office Action, page 3):



3,7-bis(4-nitrophenethyl)-3,7-diazabicyclo[3.3.1]nonane

The aforementioned compound is referred to in the discussion below as "the Andersson compound."

The Office goes on to state:

The difference between the instant claim and the prior art compound is that the instant claim replaces one H of the prior art compound with H<sup>3</sup>. ...

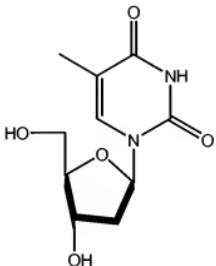
One having ordinary skill in the art would be motivated to modify the compound of Anderson et al. to obtain the instant claimed compound. Because it is well known in the art to replace a hydrogen in a known compound with H<sup>3</sup> to see how the compound would work in the body. Rai et al. replace H by H<sup>3</sup> on the thymidine to follow how the drug is used in the body.

This is respectfully traversed.

[2] Andersson

The Andersson compound is one of over 200 compounds disclosed in Andersson. More specifically, the Andersson compound is found within a long list of compounds spanning pages 67-80 of Andersson. Many of the compounds disclosed in Andersson contain a benzonitrile moiety. The Andersson compound, on the other hand, does not contain such a moiety and is one of only two compounds that is substituted with a nitro group. Andersson does not specifically provide biological data for the Andersson compound itself. The Andersson compound also does not appear to have been one of the compounds that was characterized by mass spectrometry.

[3] Rai discloses the use of (methyl-<sup>3</sup>H)-thymidine as an estimator of bacterial growth in-situ. For purposes of clarification, the chemical structure of thymidine itself is shown below:



Rai, however, does not provide a method of synthesizing the tritiated thymidine used in the aforementioned studies.

[4] The Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353, 1358 (2008) discussed the requirements for establishing whether a claimed compound is *prima facie* obvious over a reference compound (emphasis added):

The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 (“Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.”). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a “finite number of identified, predictable solutions,” 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this “easily traversed, small and finite number of alternatives ... might support an inference of obviousness.” To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these “identified, predictable solutions” may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

**In other words, post- *KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.**

[5] Applicants submit that the teachings of the prior art of record would not have led one to select the Andersson compound as a lead compound, much less modify the Andersson compound in the manner needed to arrive at the claimed compounds. This is discussed in more detail below.

[A] The Andersson compound is one of over 200 compounds disclosed in Andersson. More specifically, the Andersson compound is found within a long list of compounds spanning pages 67-80 of Andersson. Many of the compounds disclosed in Andersson contain a benzonitrile moiety. The Andersson compound, on the other hand,

does not contain such a moiety and is one of only two compounds that is substituted with a nitro group. Andersson does not specifically provide biological data for the Andersson compound itself. The Andersson compound does not appear to have been one of the compounds that was characterized by mass spectrometry.

**[B]** Even if one would have been led to the Andersson compound (and Applicants do not concede that this is the case here), there is nothing in the prior art of record that would have led one to modify the Andersson compound in the manner required by the claims. This is discussed in more detail below.

According to the specification (page 5, lines 10-18 of the Specification, underline emphasis added):

The successful use of a radioligand compound in a binding assay relies on a number of parameters including the affinity of the radioligand for the channel of interest as well as the off rate of the compound once it has bound. Ideally a suitable radioligand will have an affinity that allows competition with a candidate compound which can bind the same site as well as an off rate that allows the radioligand to remain in contact long enough for its binding to be detectable. These properties in a compound cannot be predicted. Accordingly, the present invention relates to the finding that a 1, 2 or 3 tritium substituted compound of Formula I or a compound of Formula II can be synthesised and is suitable for use in a competitive binding assay.

There are multiple sites on the Andersson compound where one could potentially replace a hydrogen atom with tritium. However, there is nothing in the prior art of record that would have led one to predict what level and location of tritium incorporation would have resulted in “an affinity that allows competition with a candidate compound which can bind the same site as well as an off rate that allows the radioligand to remain in contact long enough for its binding to be detectable.” There are no tritiated compounds disclosed in Andersson. The only tritiated compound disclosed in Rai is (methyl-<sup>3</sup>H)-thymidine, which is structurally quite a bit different from the claimed compounds-- thymidine does not even contain a phenyl ring. Moreover, the tritium label in (methyl-

<sup>3</sup>H)-thymidine is located in a methyl group and not in ring. In fact, the tritium label is not even found in an sp<sup>2</sup> carbon for that matter.

In view of these facts, it would not have been obvious to select the Andersson compound as a lead compound for further study. Accordingly, it also would not have been obvious to a person of ordinary skill in the art to make any kind of variant of the Andersson compound. Thus, one of ordinary skill in the art would not be motivated by Andersson to prepare the claimed compounds for at least this reason. In addition, since it would not have been obvious to make the claimed compounds, it also would not have been obvious to use the claimed compounds in the methods claimed in claims 4-10.

[6] Applicants now turn to claims 11-13. Claim 11 is directed to a process for preparing the claimed compounds, which includes tritiating 3,7-Bis[2-(4-nitrophenyl)ethyl]-3,7-diazabicyclo[3.3.1]nonane in the presence of (1,5-cyclooctadiene)bis(methylidiphenyl-phosphine)iridium(I) hexafluorophosphate. The claimed process requires the use of the Andersson compound, which contains readily reducible nitro groups. The inventors were nonetheless still able to incorporate the tritium label and obtain high specific activity without accompanying reduction of the nitro groups to amino groups. In short, the claimed methods produced an unexpected result.

“Evidence rebutting a prima facie case of obviousness can include: ‘evidence of unexpected results,’ [citation omitted] (*In re Sullivan* 498 F.3d 1345, 1351 (Fed. Cir. 2007)). Applicants submit that the foregoing is evidence that the claimed methods would not have been obvious to a person of ordinary skill in the art at the time the invention was made. As such, Applicants respectfully request that the rejection be reconsidered and withdrawn for at least this reason.

CONCLUSION

Applicants submit that all claims are in condition for allowance.

The fee in the amount of \$130 for the one month extension of time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-504US1 / 100974-1P US.

Respectfully submitted,

Date: January 23, 2009

/John T. Kendall/

John T. Kendall, Ph.D.  
Reg. No. 50,680

Fish & Richardson P.C.  
225 Franklin Street  
Boston, MA 02110  
Telephone: (617) 542-5070  
Facsimile: (877) 769-7945